3. Price, J. M., et al.: Bladder tumors in rats fed cyclohexylamine or high doses of a mixture of cyclamate and saccharin. Science 167: 1131–1132 (1970).
4. Bryan, G. T., Erturk, E., and Yoshido, O.: Production of urinary bladder carcinoma by sodium saccharin. Science 168: 1238–1240 (1970).
5. Food and Drug Administration, Division of Pathology: Histopathologic evaluation of tissues from rats following continuous dietary intake of sodium saccharin and calcium cyclamate for a maximum period of two years. Final report, project P–169–170. Washington, D. C., Dec. 21, 1973.
6. Hicks, R. M., and Chowaniec, J.: The importance of synergy between weak carcinogens in the induction of bladder cancer in experimental animals. Cancer Res 37: 2943–2949 (1977).
7. Saccharin and its salts. Federal Register 42: 19996–20006, No. 73, pt. III, Apr. 15, 1977.
8. Burbank, F., and Fraumeni, J. F.: Synthetic sweetener consumption and bladder cancer trends in the United States. Nature 227: 293–294 (1970).
9. Armstrong, B., and Doll, R.: Bladder cancer mortality in England and Wales in relation to cigarette smoking and saccharin consumption. Br J Prev Soc Med 28: 233–240 (1974).
10. Kessler, I. I.: Cancer mortality among diabetics. JNCI 44: 673–686 (1970).
11. Armstrong, B., and Doll, R.: Bladder cancer mortality in diabetics in relation to saccharin consumption and smoking habits. Br J Prev Soc Med 29: 73–81 (1975).
12. Armstrong, B., et al.: Cancer mortality and saccharin consumption in diabetics. Br J Prev Soc Med 30: 151–157 (1976).
13. Kessler, I. I.: Non-nutritive sweeteners and human bladder cancer: preliminary findings. J Urol 115: 143–146 (1976).
14. Wynder, E. L., and Goldsmith, R.: The epidemiology of bladder cancer: a second look. Cancer 40: 1246–1268 (1977).
15. Howe, G. R., et al.: Artificial sweeteners and human bladder cancer. Lancet No. 8038: 578–581, Sept. 17, 1977.
16. Morgan, R. W., and Jain, M. G.: Bladder cancer: smoking, beverages, and artificial sweeteners. Can Med Assoc J 3: 1067–1070 (1974).
17. Simon, D., Yen, S., and Cole, P.: Coffee drinking and cancer of the lower urinary tract. JNCI 54: 587–591 (1975).
18. Hoover, R. N., and Strasser, P. H.: Artificial sweeteners and human bladder cancer—preliminary results. Lancet No. 8173: 837–840, Apr. 19, 1980.
19. Morrison, A. S., and Buring, J. E.: Artificial sweeteners and cancer of the lower urinary tract. New Engl J Med 302: 537–541, Mar. 6, 1980.
20. Morrison, A. S., et al.: Artificial sweeteners and bladder cancer in Manchester, U. K. and Nagoya, Japan. Br J Cancer 45: 332–336 (1982).
21. Jensen, O. M., and Kamby, C.: Intra-uterine exposure to saccharin and risk of bladder cancer in man. Int J Cancer 29: 507–509 (1982).
22. Cartwright, R. A., et al.: The epidemiology of bladder cancer in West Yorkshire. A preliminary report on nonoccupational aetiologies. Carcinogenesis 2: 343–347 (1981).

Thyroid Tumors Associated with Radiation Exposure

CHARLOTTE SILVERMAN, MD, DrPH

Dr. Silverman is Associate Director for Human Studies, Office of Science and Technology, Center for Devices and Radiological Health, Food and Drug Administration. This paper is based on one presented at the Second Binational Symposium: United States-Israel, held October 17–19, 1983, in Bethesda, Md.

Tearsheet requests to Dr. Silverman, HFZ–104, 5600 Fishers Lane, Rockville, Maryland 20857.

Synopsis

Epidemiologic studies of medically and environmentally exposed populations have been central to establishing ionizing radiation as a cause of malignant and benign thyroid tumors. Issues currently under investigation concern low dose effects, age sensitivity, the relative effectiveness of X-rays and iodine-131 in inducing thyroid cancer, and other risk factors. Excess thyroid tumors continue to appear in irradiated populations under study more than three decades after exposure.

THREE HISTORICAL EVENTS are related to the study of radiation-induced thyroid disease:

- the discovery of X-rays (external radiation) and radioactivity (internal and external radiation) at the end of the 19th century, followed almost immediately by worldwide medical applications;
- the discovery of nuclear fission in 1939, followed by atomic bomb explosions in 1945 and later atmospheric tests; and
- the production of radioactive iodine in 1942, followed by manufacture and widespread use of iodine-131 in 1946.

Beginning in the early 1920s, for more than 30 years it was common medical practice to use ionizing radiation to treat a variety of benign nonthyroid conditions of the head, neck, and upper thorax of infants and children. These conditions included enlarged thymus gland, hypertrophic tonsils and adenoids, cervical adenitis, ringworm, and acne. Unfortunately, the thyroid gland fre-

'The risk of thyroid neoplasia following external X-ray irradiation of the thyroid has been conclusively demonstrated in epidemiologic studies and in animal experiments.'

quently received direct or scatter radiation during treatments. Short-term results appeared to be excellent, and large numbers of people, possibly several million worldwide, received radiotherapy for these conditions.

The association between irradiation of the thyroid gland and thyroid malignancy was first suggested in 1950. Clinicians reported that among 28 children and young adults with thyroid cancer, 10 had histories of treatment with X-rays for thymic enlargement 4–19 years earlier, when they were less than 18 months old (*1*). A number of small studies and reviews followed this report, many confirming the association. There was, nevertheless, hesitancy to incriminate prior X-ray treatment as the cause of the observed thyroid cancers. At the time, only leukemia and skin cancer were recognized as radiation-induced and had been experimentally confirmed; the thyroid gland was considered radioresistant. The first fairly large cohort study of the late effects of X-ray treatment for thymic enlargement compared 1,400 children treated between 1926 and 1951 with 1,795 untreated siblings and with the general population of New York State. The study was published as a preliminary report in 1955 and revealed a significant increase of thyroid cancer in the treated group (*2*). Experimental verification soon followed.

Potential adverse effects from exposure of the thyroid gland to nonmedical radiation sources were first mentioned in connection with radioactive fallout from nuclear explosions. The importance of fallout radioiodine from atmospheric testing at the Nevada nuclear test site was recognized around 1954, when radioiodine was found in the thyroid glands of dairy cattle nearby. Later, researchers identified milk as the principal source of iodine-131 and children as the critical segment of the population (*3*). A cohort study of children in Utah, Nevada, and Arizona undertaken in 1964 was inconclusive, as were other later investigations and analyses. In 1954, accidental radioactive fallout occurred on three inhabited atolls of the Marshall Islands in the Pacific, and thyroid nodules began to appear among the residents 10 years later. In the past several years, the issue of the carcinogenic effects of fallout radiation has been reopened, and an expanded epidemiologic study of residents of the American Southwest is now in progress. In addition, the many military and other participants in nuclear tests at the Nevada test site and in the Pacific are the subjects of an ongoing mortality followup study. In Hiroshima and Nagasaki, a detectable excess of thyroid tumors was first noted in the atomic bomb survivors 16 years after the detonations of 1945; a significant excess was noted a decade later.

Childhood Exposure and Thyroid Neoplasia

Although the topic of radiation-associated thyroid tumors concerns all age groups, at the present time there is relatively little information about the oncogenic effects of adult exposure. Followup studies of the consequences of radiation exposure during infancy and childhood provide the most abundant and long-term data for risk analysis. A number of epidemiologic cohort studies with thyroid gland dose data permit direct estimation of risk (*4*). The researchers examined both external and internal radiation exposures under differing circumstances and at various absorbed dose levels and dose rates. The investigations included studies of thymic-irradiated children in the Rochester, N.Y., area (*5*) and in Ann Arbor, Mich. (*6*); studies of X-ray epilation for tinea capitis in Israel (*7,8*) and in New York City (*9*); the study of atomic bomb survivors in Japan (*10*); and the followup of residents of the Marshall Islands exposed to radioactive fallout (*11*). In these studies, the mean period of observation ranged from 20 to more than 30 years.

A significant excess of malignant tumors of the thyroid was found in all of the studies of childhood exposure except the tinea capitis study in New York City (*9*) and the thymic enlargement study in Ann Arbor (*6*). The exposed group in the New York City tinea study included only 288 females (13 percent), a small number of the most susceptible subgroup. In the Ann Arbor thymus study, investigators found one thyroid cancer diagnosed in a boy 9 years old who was among the 958 persons exposed as infants, a finding that was not statistically significant when compared with general population rates. There have been no followup reports of the Ann Arbor study. A significant excess of benign thyroid tumors was reported in all studies except the investigations of Japanese atomic bomb survivors, which did not report on benign lesions.

In the studies, estimated absolute risks of radiation-induced thyroid malignancy following early exposure ranged from 2.1 to 6.1 cases per million children per rad per year. The estimates were within the overall range of 1.6–9.3 cases in the 1972 and 1980 National Research Council's reports based on extrapolations from studies at higher doses (*12*). Benign adenomas generally occurred two to three times more frequently than malignant neoplasms. Risk estimates remain tentative because tumors

continue to appear in the irradiated populations under extended followup.

Radiation Factors

Thyroid dose. The induction of thyroid neoplasia has been studied over a wide range of estimated doses, from 6 to about 1,500 rad. There are uncertainties in the derivation of dose estimates in each of the studies. In some studies there appears to be a dose-response relationship. The carcinogenic thyroid dose of 9 rad estimated in the Israel tinea study is unexpectedly low. Such a low dose directs attention to the levels of radiation used in some diagnostic procedures, particularly diagnostic nuclear medicine procedures in which iodine-131 is used for thyroid imaging and function tests.

External versus internal radiation. External radiation is radiation from a source outside the body, and internal radiation comes from a source within the body as a result of deposition of radionuclides in body tissues. The risk of thyroid neoplasia following external X-irradiation of the thyroid has been conclusively demonstrated in epidemiologic studies and in animal experiments.

The tumorigenic risk of exposure of the thyroid to internal sources of radiation, principally iodine-131, is less clear. Early animal experiments suggested that iodine-131 is 10 times less effective than X-rays in inducing thyroid cancer (*13*). Data from a more recent large animal study by the Food and Drug Administration (FDA), however, did not show differences in the effectiveness of iodine-131 and X-rays in the induction of thyroid malignancy (*14*). Among irradiated female rats there were no differences in response to the two forms of radiation from 80 up to 1,000 rad. The histologic types of thyroid carcinoma, papillary and follicular, were similar to those found in human studies.

Epidemiologic studies in progress may provide some of the quantitative human data needed to clarify differences in outcomes between external and internal radiation exposure. The recently reopened and expanded study by the University of Utah and collaborators, supported by the National Cancer Institute, is examining residents of the Southwestern United States who were exposed to low-dose, internal fallout radiation from iodine-131 during the period of atmospheric bomb tests. Another study is being conducted by FDA with the assistance of the Nuclear Regulatory Commission and the National Cancer Institute. The study is designed to investigate a possible association between exposure to relatively low doses of iodine-131, such as those used in the medical diagnosis and evaluation of thyroid function in children and adolescents, and the development of thyroid neoplasms. A third study in progress is the continuing followup in Sweden of more than 10,000 mainly adult patients who received iodine-131 for diagnostic purposes for a suspected malignant thyroid tumor or thyroid dysfunction (*15*).

'Without exception, radiation-induced thyroid tumors occur more frequently in females than in males—up to a fourfold difference in incidence.'

Host Factors

Sex. Without exception, radiation-induced thyroid tumors occur more frequently in females than in males—up to a fourfold difference in incidence. The sex difference holds for almost all thyroid disease and is thought to be related to the fluctuating hormonal status of females. Differences in the sex distribution of study subjects may contribute to differences in findings, as in the two low-dose tinea capitis studies (*7–9*). Failure to find thyroid cancer in the New York City study but not in the Israeli study may be related in part to the small proportion of females in the New York study.

Age. The sensitivity of infants and children to radiation-induced neoplasia is established, and in the Israeli tinea study an enhanced risk of cancer was noted in girls irradiated when they were less than 6 years old. In contrast to the many studies of thyroid tumors following childhood irradiation, however, there have been few investigations of the effects of adult exposures. In an ongoing Swedish study of iodine-131 used diagnostically, no increase in the incidence of malignant thyroid tumors has been found to date after a mean followup period of 17 years (*15*). Of the group of 10,133 patients who received diagnostic doses of iodine-131 between 1952 and 1965, 95 percent were adults.

Among the Japanese atomic bomb survivors, excess thyroid cancers have been found in the total exposed group, but data have not yet been published on differences by age (*10*). On the island of Ronegelap in the Marshall Islands, a lower incidence of thyroid cancer in those exposed as children than in those exposed as adults is thought to result from very high doses causing excessive cell destruction in the children (*11*). In the two largest cohort studies of adults who received iodine-131 for the treatment of hyperthyroidism, increased risks of thyroid cancer have not been observed to date (*16,17*). However, followup periods have not been adequate, and

Epidemiologic studies had a primary role in establishing the association between thyroid tumors and radiation exposure, identifying risk factors and low-dose effects, stimulating animal studies, and pointing to public health implications.

the extremely large doses of iodine-131 administered for therapy (thousands of rads) may have killed thyroid cells before malignant changes could develop.

Ethnic background. The possibility of increased susceptibility to cancer development among Jewish study subjects was recently reexamined in the total study group of thymus-irradiated infants in Rochester, N.Y., and confirmation of an increased risk in the Jewish component of the study group was reported (*5*). On the other hand, in the Israeli tinea capitis study, in which the entire study population was Jewish, there were sharp differences related to country of birth.

Latent period. A minimal latent period for thyroid cancer induction of about 5–10 years and a peak incidence 15–25 years after exposure are suggested by reports now available. New cases are still coming to light, some 40 years post irradiation, as the major studies continue followup surveys. Latency appears to be unrelated to dose, and correlation with age cannot be made at this time. For adenomas, minimal latency appears to be about 10–15 years, a longer period than for malignancies.

Types of thyroid disease. Radiation-induced malignancies are indistinguishable from other thyroid cancers. Radiation-induced thyroid carcinomas in humans, like similar carcinomas in experimental animals, are primarily of the papillary or follicular or mixed types and are generally successfully treated. The small occult thyroid tumors found frequently at autopsy in the Japanese group have no demonstrated clinical significance to date. When study methods permitted the detection of benign tumors, radiation-induced thyroid adenomas were found in all the study populations in whom thyroid cancer was induced. The increase of adenomas after irradiation was about three times greater than that of carcinomas. There is no evidence that adenomas are precursors of malignancies. Other important thyroid diseases, such as hypothyroidism and acute thyroiditis, seem to be associated with higher doses of radiation than those commonly leading to neoplasia.

Comment

Epidemiologic studies have played a primary role in establishing the association between thyroid tumors and radiation exposure, identifying some of the risk factors, stimulating experimental animal studies, revealing low-dose effects, and pointing to public health implications.

Because there are no pathognomonic signs to distinguish thyroid tumors induced by radiation from those unrelated to radiation, it is difficult to estimate the contribution of radiation exposure to all thyroid tumors. An analysis of thyroid cancer data from the Connecticut Tumor Registry for the years 1935–75 shows a pattern of increase in incidence that coincides with the extensive use of radiation therapy for benign head and neck conditions among children from the early 1920s to the late 1950s (*18*). Cancer of the thyroid is responsible for approximately 1 percent of all cancer cases in the United States, with an estimated annual incidence of about 10,000 new cases. Fortunately, treatment is effective and mortality is low; the estimated 1,000 annual deaths in the United States are largely due to an extremely malignant form of thyroid carcinoma. Present knowledge is adequate to reduce the number of future cases of radiation-induced cancer.

References

1. Duffy, B. J., Jr., and Fitzgerald, P. J.: Cancer of the thyroid in children: a report of 28 cases. J Clin Endocrinol 10: 1296–1308 (1950).
2. Simpson, C. L., Hempelmann, L. H., and Fuller, L. M.: Neoplasia in children treated with x-rays in infancy for thymic enlargement. Radiology 64: 840–845 (1955).
3. Hanson, W. C.: Contamination of soft tissues of infants and children with radioactive fallout as exemplified by Cs^{137} and I^{131}. Pediatrics (supp.) 41 (Pt. II): 240–256 (1968).
4. Silverman, C., and Hoffman, D. A.: Thyroid tumor risk from radiation during childhood. Prev Med 4: 100–105 (1975).
5. Hemplemann, L. H., et al.: Neoplasms in persons treated with x-rays in infancy. Fourth survey in 20 years. JNCI 55: 519–530 (1975).
6. Pifer, J. W., et al.: Neoplasms in the Ann Arbor series of thymus-irradiated children. Am Roentgenol Radium Ther Nucl Med 53: 13–18 (1968).
7. Ron, E., and Modan, B.: Benign and malignant thyroid neoplasms after childhood irradiation for tinea capitis. JNCI 65: 7–11 (1980).
8. Ron, E., and Modan, B.: Thyroid and other neoplasms following childhood scalp irradiation. *In* Radiation carcinogenesis: epidemiology and biologic significance, edited by J. D. Boice, Jr. and J. F. Fraumeni, Jr. Raven Press, New York, 1984.

9. Shore, R. E., Albert, R. E., and Pasternak, B. S.: Follow-up study of patients treated by x-ray epilation for tinea capitis. Arch Environ Health 31: 17–28 (1976).
10. Jablon, S., Belsky, J. L., Tachikawa, K., and Steer, A.: Cancer in Japanese exposed as children to atomic bombs. Lancet No. 7706: 927–932, May 8, 1971.
11. Conard, R. A.: Summary of thyroid findings in Marshallese 22 years after exposure to radioactive fallout. *In* Radiation-associated thyroid carcinoma, edited by L. J. DeGroot, L. A. Frohman, E. L. Kaplan, and S. R. Refetoff. Grune and Stratton, New York, 1977, pp. 241–257.
12. National Research Council, Advisory Committee on the Biological Effects of Ionizing Radiation: The effects on populations of exposure to low levels of ionizing radiation. National Academy of Sciences, Washington, D.C., 1972 and 1980.
13. Doniach, I.: Effects including carcinogenesis of ^{131}I and x-rays on the thyroid of experimental animals: a review. Health Phys 9: 1357–1362 (1963).
14. Lee, W., Chiacchierini, R. P., Shleien, B., and Telles, N. C.: Thyroid tumors following ^{131}I or localized x-irradiation to the thyroid and pituitary glands in rats. Radiat Res 92: 307–319 (1982).
15. Holm, L. E., Lundell, G., and Walinder, G.: Incidence of malignant thyroid tumors in humans after exposure to diagnostic doses of iodine-131. 1. Retrospective cohort study. JNCI 64: 10555–1059 (1980).
16. Dobyns, B. M., et al.: Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism. A report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. J Clin Endocrinol Metab 38: 976–998 (1974).
17. Holm, L. E., Dahlquist, I., Israelsson, A., and Lundell, G.: Malignant thyroid tumors after iodine-131 therapy. A retrospective cohort study. New Engl J Med 303: 188–191 (1980).
18. Pottern, L. M., et al.: Thyroid cancer in Connecticut, 1935–1975: an analysis by cell type. Am J Epidemiol 112: 764–774 (1980).

Abstract

FDA Perspective on Sodium

ALLAN L. FORBES, MD

This report was given at the Second Binational Symposium: United States-Israel, held in Bethesda, Md., October 17–19, 1983. The complete paper was published in the July 1983 issue of Food Technology, pages 73–77.

Sodium, an essential nutrient, is being consumed in quantities that far exceed the amount necessary for normal development and health maintenance. The public health concern about sodium is based primarily on its relationship to hypertension. The current estimate is that about 60 million people in the United States have hypertension, ranging from borderline to severe. It is not yet clear whether sodium intake is a major environmental factor in causing hypertension. Nevertheless, sodium restriction and weight reduction for the overweight hypertensive patient are among the most effective nondrug therapies for hypertension.

Sodium in the diet comes from several sources. In addition to that which occurs naturally in almost all foods, sodium comes from salt and other compounds added during food processing and from salt added in the home during cooking and at the table and from water. The total daily intake in the United States is estimated to range between 5,600 and 7,600 mg. The National Academy of Sciences-National Research Council's Estimated Safe and Adequate Daily Dietary Intake of sodium for adults is 1,100–3,300 mg. Several major professional organizations have emphasized the possible effect of sodium on hypertension or recommended lower sodium intake by Americans.

As a practical approach to lowering sodium consumption, the Food and Drug Administration in 1981 developed a predominantly voluntary program with the goals of providing more sodium information to consumers on food packages; decreasing the amount of sodium used in processed foods; improving consumer understanding of sodium labeling, along with providing greater knowledge about the relationship between sodium and high blood pressure and, ultimately, lowering the aggregate sodium consumption by the general public. Major progress has been made on this program.